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The Regulation of Fine Movements in Patients With Charcot Marie Tooth, Type Ia: Some Ideas About Continuous Adaptation

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The flexibility of the human motor system is remarkable. Even when parts of the system are damaged, the output often remains optimal or near-optimal. The neuromotor system is designed to keep the output optimal by shifting between input sources. This capability is termed the principle of continuous adaptation. This article describes an experiment in which patients suffering from a hereditary motor and sensory neuropathy, type Ia (Charcot Marie Tooth disease, type 1a), had to perform fine motor movements. We examined whether they were able to regulate these movements in spite of the fact that the somatosensory input and motor output was substantially impaired as a result of the chronic, slowly progressing neuropathy. It was predicted that these patients were able to perform fine movements as long as the movements were well known and over-learned. Furthermore, it was predicted that these patients would compensate for the loss of somatosensory information by becoming more dependent on vision. A second prediction was that the quality of the motor performance would break down when these patients had to perform a novel motor pattern. The performance of the patients ($n = 10$) was contrasted with the performance of 20 healthy subjects. The results indicated that the patients, indeed, were able to perform the over-learned movements and that their performance deteriorated significantly when they had to perform a novel motor pattern. No indication, however, could be found for visual compensation.

Key Words: motor control, adaptation, neuropathy

One of the most intriguing aspects of human motor control is its flexibility and adaptability. We can walk, jump, shuffle, dance. We can mimic pathology and

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perform an almost infinite number of silly walks, and when a selected motor strategy is no longer successful we shift immediately towards another strategy. A simple example of this flexibility is walking on the lateral side of the foot to prevent the pain of a sharp stone in the shoe; a more complex and dramatic example can be found in the mother born without arms who is feeding and fondling her child with her feet. We are adaptive machines; in a way, we are born to adapt.

This flexibility is also beautifully stated in Bernstein's famous example of the making of circular movements with an outstretched arm. These movements can be performed with equal ease in front of the body or sideward of the body. This observation is not at all trivial, since the execution of circular movements in these different forms requires the immediate recruitment of different sets of muscle groups. Bernstein (1967) argued therefore that the execution is effector-independent. It is not only the ease of these shifts, however, that is remarkable but also the fact that the movement output remains more or less the same or invariant in spite of the different muscle combinations that are used for achieving the goal. Bernstein (1967) termed this *the principle of equal simplicity*. In this context, we must also note the term *topology*. As Wiesendanger (1998) indicates, Bernstein uses the term *topology* as in "Gestalt Psychology." For him, it reflects the "shape" of a movement rather than the muscle actions. According to Bernstein, it is the topological information that is stored in the brain and not the muscle-specific details. Lashley's *principle of motor equivalence* is closely related to Bernstein's principle of equal simplicity. Lashley (1933) was amazed by the capacity of monkeys and rats to adapt to severe brain damage. Lashley observed that after almost complete destruction of both precentral gyri, the animals gave evidence of perfect retention of visual habits and manipulative skills. He saw that direct adaptive changes were made to compensate for the paretic limb. Also for Lashley, this indicated that it was not a sequence of muscle contractions that was stored but a rather abstract goal that could be reached by various means. This he called the principle of motor equivalence.

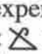
Both Lashley and Bernstein mentioned handwriting as a clearly observable example of their principles. Indeed, writing with the preferred hand or the non-preferred hand, writing small on a piece of paper or large at the blackboard requires totally different sets of muscles, but the characteristic and individual character of the writing pattern remains more or less intact regardless of the employed effector organs.

Hence, what we see here is the existence of multiple solutions for attaining a given goal, which indicates that the neural control must be flexible. Bethe (1931) introduced the *Plastizitätslehre*, in which he discussed the flexibility in the distribution and connectivity of neural networks. Bethe was convinced that the brain continuously adapts itself to cope with the changes in the body and the environment. He observed that insects, after removal of a set of legs, immediately shifted to a motor strategy employing another set of legs. Hence, he concluded, networks in the brain seem to adapt themselves to changes in the peripheral input in order to keep the output optimal. In the former Soviet Union, it was Luria (1973) who stressed the adaptability and flexibility of neural systems. He argued that functions were not pin-pointedly localized in certain areas in the brain but the result of the coordinated activity of functional systems. These functional systems consisted of a number of interconnected areas, not necessarily anatomically close to each other. Luria showed that after damaging a functional system, the system reorganizes to keep the output constant or optimal.

In the 1980s the discussion about plasticity and flexibility was reintroduced by the work of Edelman (1987), and Merzenich, Kaas, Wall, Nelson, Sur, and Felleman, (1983). Edelman (1987) stressed the fact that the dendritic structure of individual brains is highly different as a result of personal learning histories and different streams of input. Merzenich et al. (1983) showed that the representation of body surface in the central nervous system could be remodeled as a result of changing the peripheral input. They showed that after cutting the n. medianus in adult monkeys, the representation of the hand in the brain changed dramatically and that the parts of the representation that were deprived of input shriveled up. However, very soon these deprived cortical areas were taken over by areas that still received input. Numerous studies showed that cortical sensorimotor representations reorganized themselves after peripheral damage (Kaas, Merzenich, & Killackey, 1983), after amputation (Hall, Flament, Fraser, & Lemon, 1990; Hess, Mills, & Murray, 1986), after spinal cord injury (Topka, Cohen, Cole, & Hallet, 1991; Roelcke, Curt, Otte, Missimer, Maguire, Dietz, & Leenders, 1997), after de-afferentation (Brasil-Neto, Cohen, Pascual-Leone, Jabir, Wall, & Hallett, 1992), after ischaemic nerve block (Brasil-Neto, Valls-Sole, Pascual-Leone, Cammarota, Amassian, Cracco, Maccabee, Hallet, & Cohen, 1993), after stroke (Traversa, Cicinelli, Bassi, Rossini, & Bernardi, 1997) and even after arthritis-like inflammation (Dubner & Ruda, 1992). These studies reflect the adaptability of the nervous system when confronted with a novel lay-out of information and, in fact, provide a structural basis for the ideas on plasticity introduced much earlier in the 20th century.

As we know from spinal cord lesions in humans or from gait recovery after amputation, this adaptive power is less immediate and hence less dramatic at the behavioral level, but certainly not absent. De Visser, Pauwels, Duysens, Mulder, and Veth (1998), for example, showed that after limb-saving surgery whereby total bone-joint systems are removed and replaced by endo-prosthetic devices, subjects were able to relearn gait to a remarkable level, although not to their pre-morbid automated level. Also in other studies, the capacity of patients to adapt to substantial alterations of sensory input has been indicated (Geurts, Mulder, Nienhuis, & Rijken, 1992a, 1992b, 1992c; Mulder & Geurts, 1993).

On the basis of the above mentioned studies, one could argue that the neuromotor system is designed to keep the output constant or optimal, even when the information providers (peripheral damage) or processors (central damage) are impaired. In that case, the system shows a shift in control strategies. Indeed, when visual information is impaired, the role of somatosensory information becomes more crucial. When somatosensory information is impaired, the role of vision becomes more prominent (Geurts, Mulder, Nienhuis, & Rijken, 1992a; Lajoie, Paillard, Teasdale, Bard, Fleury, Forget, & Lamarre, 1992). However, from our own research, it became clear that, in the aforementioned case, a number of subjects also showed shifts to a cognitive or attention-driven mode of control (Geurts & Mulder, 1994). Hence, the type of shift seems to be individual-specific.

The present article describes a novel experiment in which this capacity to keep the output optimal was studied. The experiment was performed with patients suffering from Charcot Marie Tooth disease, type Ia (CMT-Ia). These patients suffer from a hereditary sensory and motor neuropathy, leading to severe motor and sensory impairments. Since it is known that somatosensory information plays an important role, not only in the regulation of slow movements but also in the regulation of fast and highly coordinated movements such as speaking and writing, it is interesting to see whether these patients are impaired in the performance of a highly coordinated fine motor skill such as handwriting (see van Doorn, & Keuss, 1993, for a more detailed discussion on the role of vision and kinaesthetic information in handwriting). In the present study, CMT patients and matched healthy controls had to perform an over-learned fine motor task (writing the number "3"). They had to write the "3" with eyes open, with eyes closed, and in a condition where the somatosensory information was even more impaired by using an ischaemic block (pressure cuff). In a second part of the experiment, they had to perform a novel motor pattern (writing a novel grapheme: ) under the same conditions.

The following, rather specific hypotheses are tested: (a) Normal writing (eyes open, no ischaemic block) will not be impaired in these subjects. Indeed, the duration of the disease and its slowly progressing character has given the neural system ample time to reorganize its output. (b) Performing a new motor pattern, however, will be compromised by the neuropathy. The rationale for the latter hypothesis can be found in earlier work performed by Geurts, Mulder, Nienhuis, and Rijken (1992b). They showed, for example, that these CMT-Ia patients showed no shift toward visual dependency and attention-driven control in the performance of a simple standing-balance task. They were able to use the impaired somatosensory information for controlling their balance in a way not distinguishable from controls. However, as soon as they were fit with orthopedic shoes that altered the afferent information, they showed significant and immediate shifts toward a visual- and attention-driven control strategy (Geurts, Mulder, Nienhuis, & Rijken, 1992c). Hence, novelty seems to be a relevant factor for tapping the adaptability of the neuromotor system.

(c) Since the somatosensory information is impaired in CMT patients, it is expected that they will shift toward a control strategy that depends highly on visual information. It is therefore predicted that CMT patients will be hindered disproportionally by withdrawing the visual information but not by compromising the sematosensory information because, across the years, they have learned to cope with this impaired input source.

Method

Subjects

Twenty neurologically normal right handed subjects (10 male, 10 female) ranging in age from 18 to 55 years (mean age = 27.7) volunteered for the study. None of the subjects had any cardiovascular problems, diabetes mellitus, or other diseases that could have interfered with the study. None of them showed any mechanical impairments of the arm, hand, or wrist. All healthy subjects were right-handed.

Ten patients with Charcot Marie Tooth, type Ia (6 male, 4 female) ranging in age from 15 to 55 years (mean age = 31) participated in the study. The patients were included on the basis of their Mean Nerve Conduction Velocity (MNCV). This MNCV had to be lower than 38 m/s. Furthermore, genetically all patients had to show a segmented duplication at chromosome 17p11.2. None of the patients suffered from other diseases that interfered with the aim of the present study. All patients were right-handed.

All subjects gave their written informed consent and the study has been approved by the local medical ethics committee.

Procedure

Subjects were seated comfortably in a high backed chair in front of a digitizer (Calcomp 2500), which was positioned horizontally on a table. Writing and drawing took place on normal paper with a "normal" ballpoint, connected wirelessly to the digitizer. The digitizer recorded the position of the pen-tip in the X and Y direction. The position of the pen on the digitizing tablet was recorded with a frequency of 100 Hz and a spatial accuracy of 0.2 mm. The digitizer was connected to a Compacq Deskpro 590 computer. Subjects were instructed to write as fast and accurate as possible the number "3" in empty boxes of 10 × 10 mm. The writing of the number had to be repeated 25 times. The same instruction was given in relation to the drawing of the novel grapheme (). Also the drawing had to be repeated 25 times. The order of the trial blocks (25 numbers, 25 graphemes) was randomized across the subjects. The right lower arm was immobilized by a lightweight splint firmly secured to the table top. The splint left the movements of the wrist, hand, and fingers unconstrained. The immobilization device prevented any compensatory movements of the upper arm and/or shoulder. The session started with a basic or reference condition, in which subjects had to write a "3" or to draw the grapheme while vision was available and without any somatosensory manipulation.

The somatosensory input was manipulated by using a sphygmanometer cuff that was inflated up to 200 mm Hg. Before the start of the experiment, the cuff was already applied to the right upper arm, but it was inflated only during the cuff-condition. After 10 min of cuff inflation, the cuff condition started. The effect of the cuff on the quality of the somatosensory feedback was evaluated by testing the vibratory sense. When the duration that the vibrations (128 Hz) could be sensed had been decreased to less than 15 s, the condition started. After the cuff condition, the subjects had a pause of at least 15 min to recover. The visual information was blocked by using a shield that covered the moving hand.

The parameters that were recorded during the writing and drawing tasks were velocity (cm/s), pressure on the pen-tip in grams, and movement fluency. Fluency was determined in terms of the number of acceleration-deceleration phases within a certain time-interval. When the number is increasing, this is seen as an indication of an increasing dysfluency.

Hence, the fine motor performance of CMT patients and healthy controls was studied in the following conditions: writing a "3" or a grapheme, with vision and without any manipulation of the somatosensory feedback (CONTROL); writing a "3" while somatosensory information was impaired (CUFF); writing a "3" while the moving hand was invisible (NO-VISION), and in a final condition the somatosensory information was manipulated while vision was also blocked (CUFF/NO-VISION).

Results

A MANOVA for repeated measurements has been performed in which the figure "3" and the grapheme have been analyzed simultaneously, and indicated by the factor *Figure*. The other factors are: *VISION (with/without)*, *CUFF (with/without)*, with *GROUP* as a between factor. The number of control subjects has been reduced to 18 since, due to a technical problem, more than 50% of the data were missing for 2 subjects.

The over-all results show a significant effect of somatosensory manipulation (CUFF) on velocity ($F_{1,26} = 17.171$, $p < .001$). Furthermore, blocking the visual information while writing resulted in significant effects on velocity ($F_{1,26} = 34.731$, $p < .001$, on dysfluency ($F_{1,26} = 14.561$, $p < .001$) and on pen-pressure ($F_{1,26}$ =

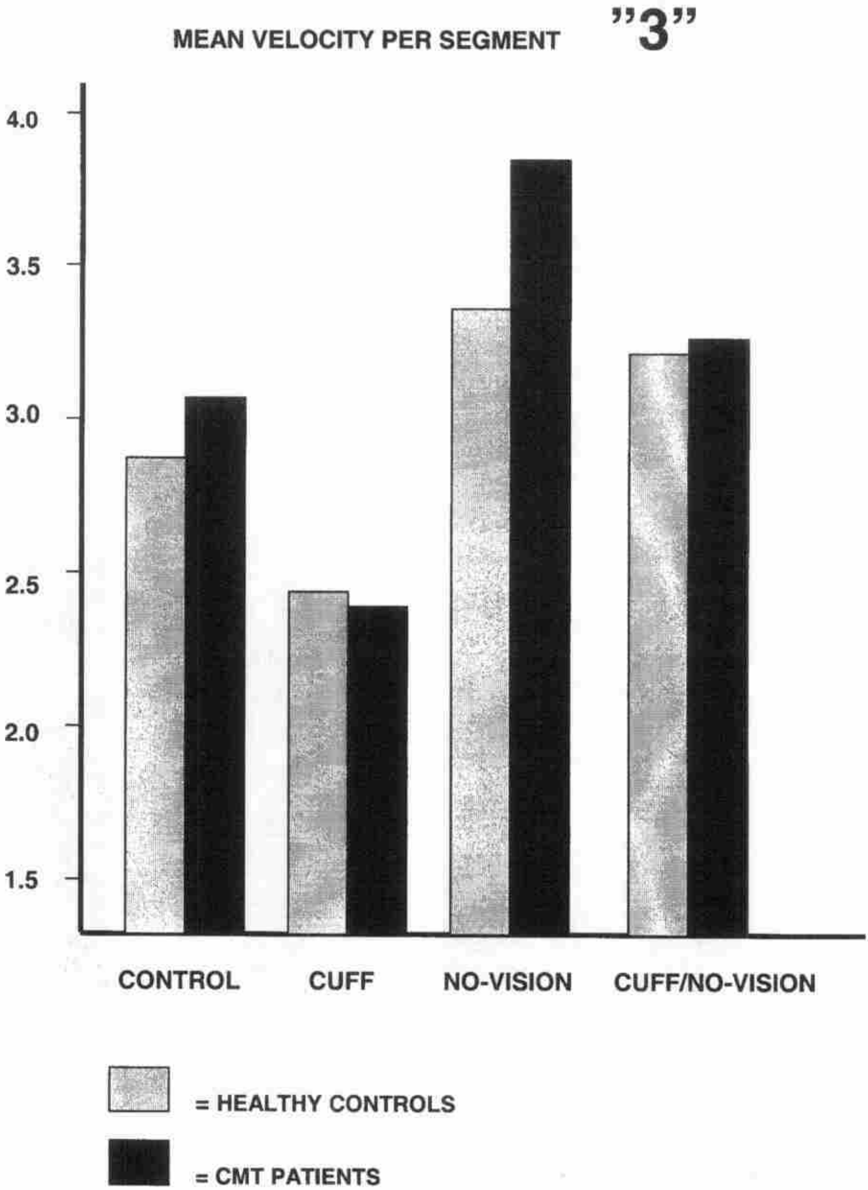


Figure 1 — The mean velocity of the writing movements in the production of an overlearned motor pattern. The velocity is expressed in cm/s. (See text for explanation of the used experimental conditions.)

10.892, $p = .003$). The difference between writing the over-learned "3" and producing a novel grapheme was significant for velocity ($F_{1,26} = 10.660$, $p < .003$), for dysfluency ($F_{1,26} = 40.812$, $p < .001$), and for pen-pressure ($F_{1,26} = 27.077$, $p < .001$). A significant Group × Figure interaction was found only for dysfluency ($F_{1,26} = 11.210$, $p = .003$). The difference between the groups of patients and controls were significant for dysfluency ($F_{1,26} = 18.509$, $p < .001$) but not for velocity ($F_{1,26} = .019$, $p = .893$) and pen pressure ($F_{1,26} = 2.604$, $p = .118$).

Writing the "3". For observing the data in more detail, we first focus at writing the "3". The results in terms of velocity, pressure on the pen-tip, and fluency are presented.

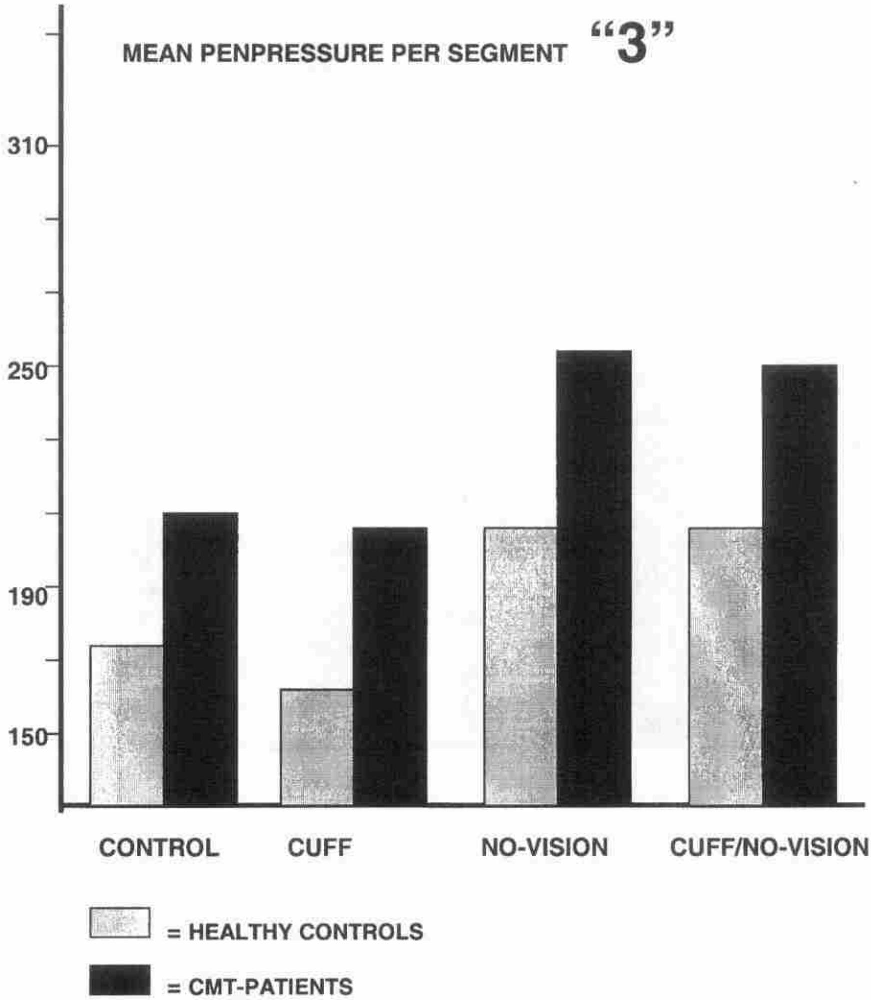


Figure 2 — The mean pressure on the tip of the pen while producing an overlearned motor pattern. The pressure is expressed in grams. (See text for explanation of the used experimental conditions.)

Velocity (cm/sec). Figure 1 shows the effects of the somatosensory manipulation (CUFF), the visual manipulation (NO-VISION), and the combined somatosensory and visual manipulation (CUFF/NO-VISION). These results are compared with the results obtained under the optimal performance condition (CONTROL).

The results indicated that no significant difference in velocity existed between the CMT-patients and the healthy controls in the optimal or reference condition (CONTROL). The results further indicated a general and significant effect of the somatosensory manipulation on velocity ($F_{1,26} = 29.009$, $p < .001$). However,

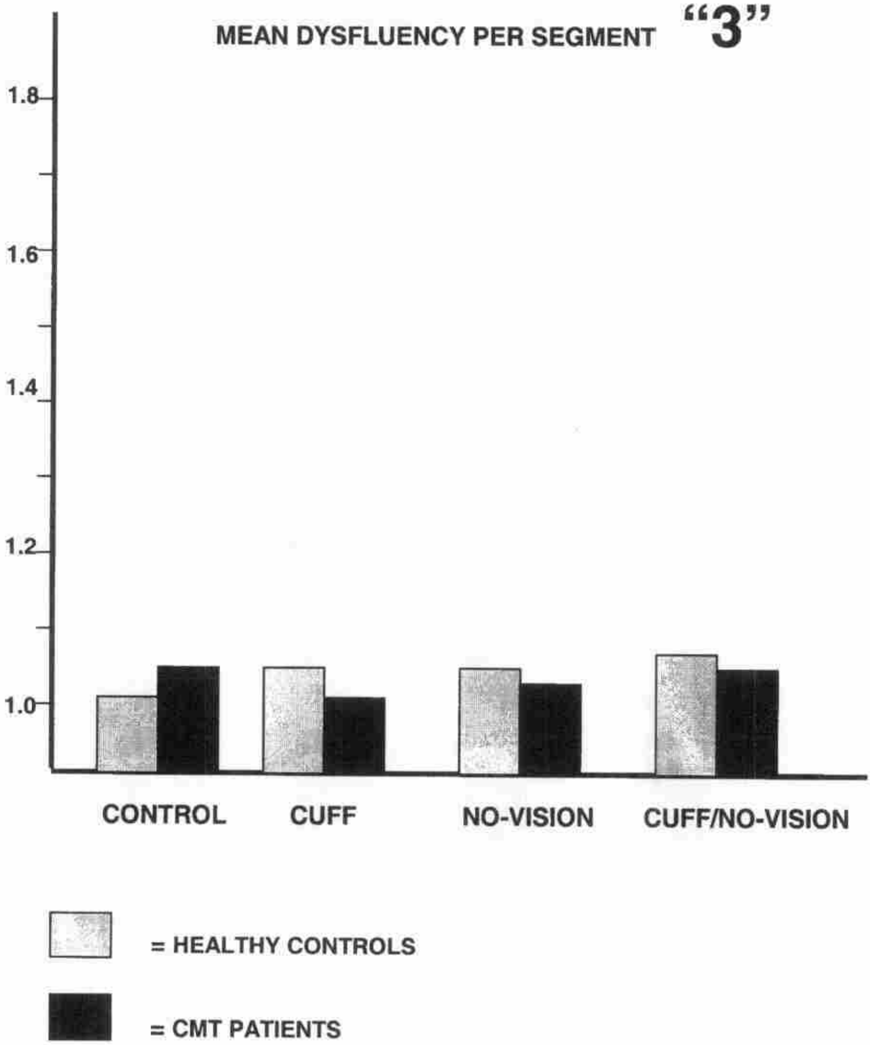


Figure 3 — The mean dysfluency per movement segment while producing an overlearned motor pattern. The dysfluency is expressed as the number of accelerations and decelerations per time interval. The higher the number, the more dysfluent the movement pattern. (See text for explanation of the used experimental conditions.)

no significant interaction between Group (patients/controls) × Cuff could be obtained, indicating that patients as well as healthy controls were hindered in the same manner by the impaired somatosensory feedback. The blocking of the visual information while writing the "3" resulted in a significant increase of velocity ($F_{1,26} = 24.623$, $p < .001$), but again, no significant Group × Vision interaction could be obtained. The condition in which the manipulation of the somatosensory information was combined with the blocking of the visual information revealed no significant effect on velocity.

Pen Pressure (g). Figure 2 shows the effects of the 4 conditions on pen-pressure.

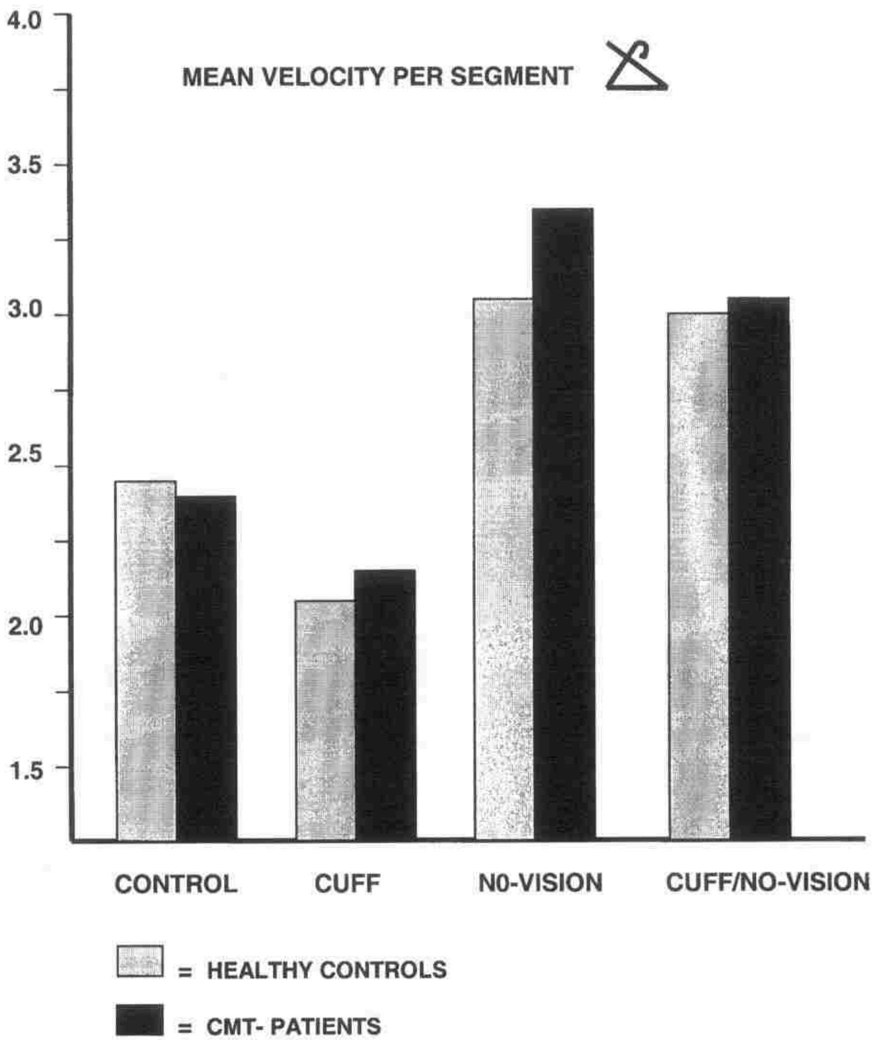


Figure 4 — The mean velocity of the movements while producing a novel motor pattern. The velocity is expressed in cm/s. (See text for explanation of the used experimental conditions.)

The results indicate that only the visual manipulation had a significant effect on pen-pressure ($F_{1,26} = 10.005$, $p < .004$). None of the interactions were significant.

Fluency (Mean Number of Accelerations and Decelerations Per Time Interval). Figure 3 shows that the patients as well as the normal subjects executed the movements quite fluently. No significant differences in fluency could be obtained.

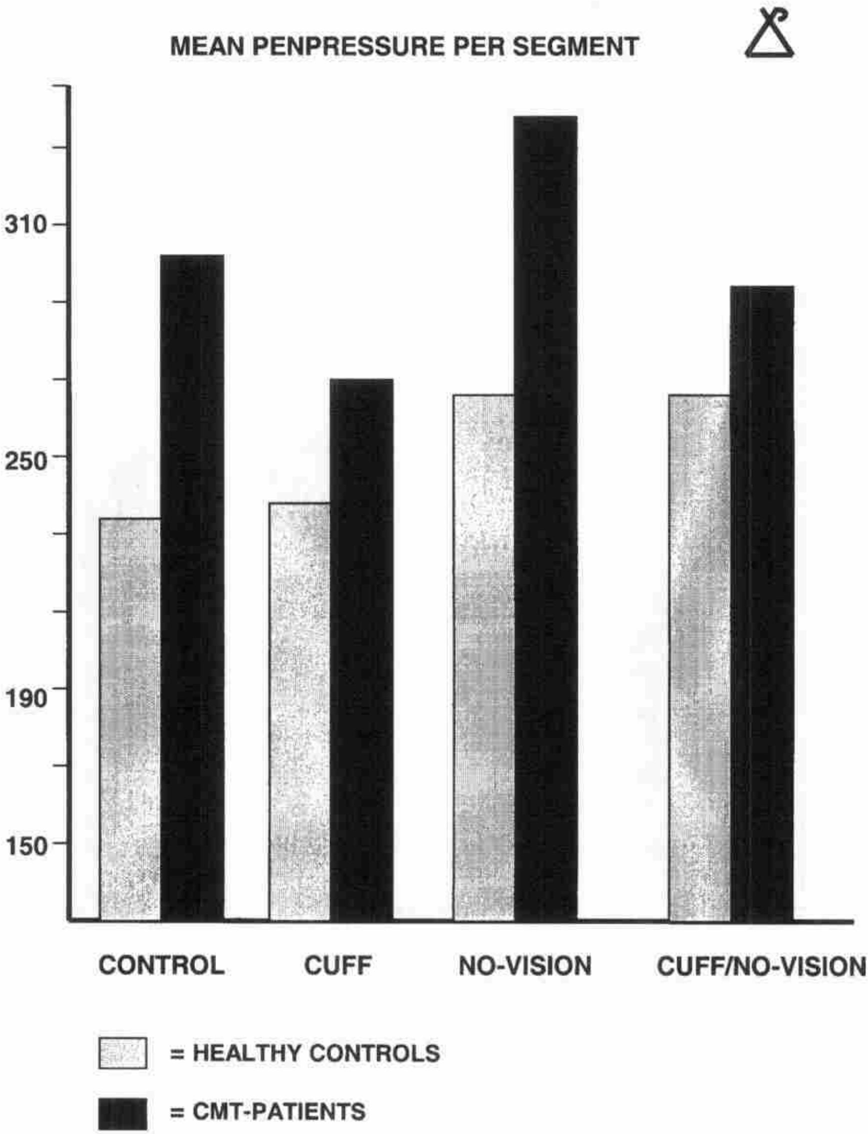


Figure 5 — The mean pressure on the tip of the pen while producing a novel motor pattern. The pressure is expressed in grams. (See text for explanation of the used experimental conditions.)

Writing the Grapheme ( ). During the grapheme session, the subject had to perform the task under the same conditions as in the "3" session. The results are discussed in terms of the similar variables: velocity, pen-pressure, and fluency.

Velocity (cm/s). Figure 4 shows the results of producing a novel motor pattern on the velocity profiles. Manipulating the somatosensory input by applying the cuff resulted in a small but significant decrease in velocity ($F_{1,26} = 17.171$, $p < .001$). The blocking of the visual input resulted in an increase in the velocity ($F_{1,26} = 46.618$, $p < .001$). None of the Group × Vision interactions were significant.

Pen Pressure (g). The results indicate no significant difference in pen pressure as a result of the cuff application ($F_{1,26} = 4.700$, $p < .038$). The No-Vision condition

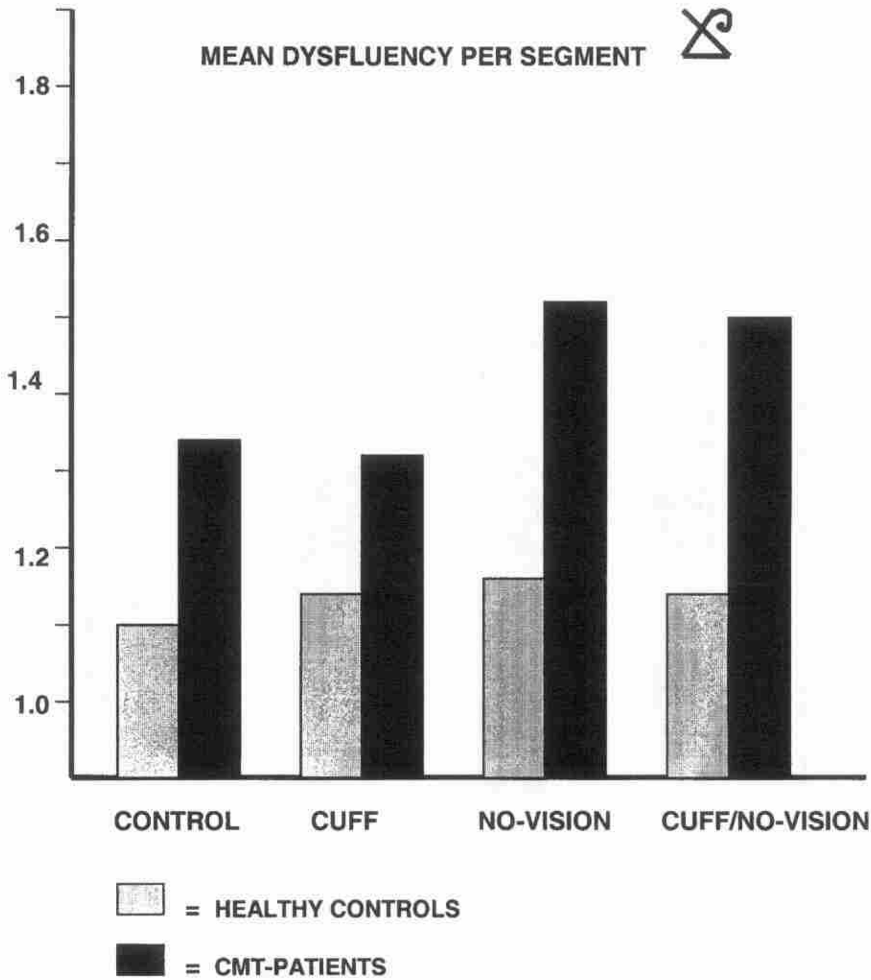
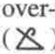


Figure 6 — Mean dysfluency per movement segment while producing a novel motor pattern. The dysfluency is expressed as the number of accelerations and decelerations per time interval. The higher the number, the more dysfluent the movement pattern. (See text for explanation of the used experimental conditions.)

resulted in a significant increase of pen-pressure ($F_{1,26} = 10.892, p < .003$). None of the other manipulations had a significant effect on pen-pressure.

Fluency (Mean Number of Accelerations and Decelerations Per Time Interval). The results indicate a significant effect of no-vision on dysfluency ($F_{1,26} = 14.561, p = .001$). Furthermore a significant Group × Figure interaction was obtained ($F_{1,26} = 11.210, p = .003$) (see Figure 6).

Discussion

Recall that the main aim of the present article was to study the adaptability of the human motor system. It was argued that the motor system was "designed" in such a way that even when parts of the system are damaged, the output remains optimal or near-optimal. Furthermore, it was argued that when peripheral information is impaired, the system is forced to shift to other sources of input. Patients with Charcot Marie Tooth were studied in this experiment because these patients clearly suffered from an impaired somatosensory input. However, as the pathology in these patients actually exists from the very beginning of life, the question was to what extend they were adapted to the pathology. Writing was selected as the experimental task since, from a motor-control point of view, writing is a very interesting task. Indeed, it is characterized by the harmonious coordination of movement elements organized in time and space. After writing has been learned during a long-term educational process, it can be performed more or less automatic, without the necessity of controlling consciously the production of each separate character. That learning to write is, indeed, a long learning process may be indicated by the fact that adult writing speed is achieved only at the age of 15 (Sassoon, Nimmo-Smith, & Wing, 1986). In the present experiment, the writing of a "3" was selected as an over-learned task, and this was contrasted with the production of a novel grapheme ().

When I am writing a "3", how do I know whether the act is performed correctly? The "3" is produced by moving the tip of the pen on and above a two-dimensional writing surface. The pen-tip makes a sequence of rapid, multi-phasic movements that are the result of contractions of muscles, located primarily in the lower arm, wrist, hand, and fingers. It is argued here that on the basis of a large number of repetitions, a neural representation of the act has been stored in the brain. This representation contains the global (or topological) information about the production of writing patterns, updated by the numerous times the "3" has been produced. In the grapheme condition, a totally different situation exists. For the grapheme, no such representation exists so that the movements here have to be produced *de novo*. Of course all subjects were able to write or draw, but it makes a difference whether you have to write or draw something very familiar or whether you have to produce a novel motor pattern. The signature is an example of this; everybody can make the movements necessary for producing a signature, but it is the personal signature only that has been automated across time. The movement characteristics of that signature are firmly represented in the brain.

The results showed that the CMT patients were perfectly able to write the "3". The experimental manipulations elicited only general effects but no significant interactions, indicating that the CMT patients and the controls solved the motor problems in more or less the same way. These results were in accordance with our prediction that CMT patients would not be hindered by their disease, since they had ample time to adapt to the sensory deficit. They had learned to "live at the minimum." What we did not expect, however, was that they did not visually compensate for the loss of somatosensory information. The blocking of the visual feedback resulted only in a general effect on velocity and pen-pressure but not in a significant Groups × Condition interaction.

The fact that the cuff-condition did not result in a patient-specific effect was not unexpected. Indeed, the CMT patients were used to the meager quality of their somatosensory input. Recall that also the cuff did not eliminate all information but that it only compromised the quality of the somatosensory information further. So in all conditions some somatosensory input was left. It seems as if the remaining proprioceptive information was still sufficient for performing the task.

None of the manipulations had any effect on fluency, which may indicate that the stability of the movement remained unaffected by these manipulations. Indeed, mature and stable movement strategies are characterized by smooth and fluent velocity profiles, showing minimal disturbances in the deceleration and acceleration phase (Hay,1979; Meulenbroek & van Galen, 1986; Wann, 1987)

As indicated the production of the grapheme differed in many aspects from the production of the well known "3". Here the exact order and topology of the movements is not familiar and over-learned; hence, no redundant representation of the motor pattern is assumed. Therefore the movement cannot be generated from some memory store but has to be constructed "on the spot." Somatosensory and visual information is necessary for producing the grapheme. The CMT-patients, however, are impaired in their on-line use of the response-produced somatosensory information. This is clearly reflected in the dysfluency profile. Although the normal controls did not loose their smoothness when drawing the grapheme, the CMT-patients were no longer able to produce the movements in a fluent way. Their fluency-profile deteriorated substantially, indicating a break down of stability. The fluency results showed also that the NO-VISION condition had a significant additional effect on the (dys-)fluency. Recall that this was not the case in the "3" task. Adding the pressure cuff to the no-vision condition, however, did not lead to any further deterioration, indicating the crucial role of vision in the drawing of the grapheme. A remarkable and not easy to understand result is presented by the fact that the velocity is not affected by the production of the grapheme. This, indeed, is surprising since in general a close relationship between velocity and fluency is found.

Although CMT-patients in general do not complain about the fine motor function, and although many clinicians claim that the control of fine movements is unimpaired in these patients, the results of the present study showed that this is only part of the story. It has been shown that the system is, indeed, able to keep the output optimal and indistinguishable from healthy controls but only in conditions that require the performance of familiar movement patterns. When a novel movement pattern has to be performed, the fluency or stability of the performance is lost.

This may have implications for neurological assessment. Indeed, when a clinician wants to establish the momentary performance level in regard to chronic (life-long) disease, requesting only well known motor tasks could be problematic. These tasks have been performed numerous times so that they "exploit" all possible control routes. Observing the performance of sensorimotor tasks, such as standing, walking, and grasping, therefore could lead to the (wrong) conclusion that nothing is wrong with the control of movements. Some caution and modesty, however, is necessary. Indeed it may be that the obtained differences were caused at least partly by the intrinsic character of the task (writing a "3" vs. drawing a grapheme). The differences in fluency could be the result of the shape of the form of the stimuli, in that the "3" elicits a more continuous movement pattern than the grapheme. However, the risk that the obtained dysfluency results are epi-phenomena of the employed stimuli is limited by the fact that fluency was defined in terms of the number of acceleration-deceleration phases in individual segments so that the fluency was measured independent of the topological structure. Nevertheless, further research is necessary in order to prove whether the obtained results of this single study can be replicated.

References

Bernstein, N.A. (1967). *The co-ordination and regulation of movements*. Oxford, UK: Pergamon Press.

Brasil-Neto, J.P., Cohen, L.G., Pascual-Leone, A., Jabir, F.K., Wall, R.T., & Hallett, M. (1992). Rapid reversible modulation of human motor outputs after transient deafferentation of the fore-arm: a study with transcranial magnetic stimulation. *Neurology,* **42**, 1302-1306.

Brasil-Neto, J.P., Valls-Sole, J., Pascual-Leone, A., Cammarota, A., Amassian, V.A., & Cracco, R. (1993). Rapid modulation of human cortical motor output following ischaemic nerve block. *Brain,* **116**, 511-525.

De Visser, E., Pauwels, J., Duysens, J., Mulder, Th., & Veth, R.P.H. (1998). Gait adaptations during walking under visual and cognitive constraints: A study of patients recovering from limb-saving surgery of the lower limb. *American Journal of Physical Medicine and Rehabilitation,* **77**, 503-509.

Dubner, R., & Ruda, M.A. (1992). Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends in Neuroscience,* **15**, 96-102.

Edelman, G.M. (1987). *Neural darwinism.* New York: Basic.

Geurts, A.C.H., Mulder, Th., Nienhuis, B., & Rijken, R.A.J. (1992a). Postural reorganization following lower limb amputation: Possible motor and sensory mechanisms. *Scandinavian Journal of Rehabilitation Medicine,* **24**, 83-90.

Geurts, A.C.H., Mulder, Th., Nienhuis, B., & Rijken, R.A.J. (1992b). Postural organization in patients with hereditary motor and sensory neuropathy. *Archives of Physical Medicine & Rehabilitation,* **73**, 569-572.

Geurts, A.C.H., Mulder, Th., Nienhuis, B., & Rijken, R.A.J. (1992c). Influence of orthopedic footwear on postural control in patients with hereditary motor and sensory neuropathy. *Journal of Rehabilitation Sciences,* **5**, 3-9.

Geurts, A.C.H., & Mulder, Th. (1994). Attention demands in balance recovery following lower limb amputation. *Journal of Motor Behavior,* **26**, 162-170.

Hall, E.J., Flament, D., Fraser, C., & Lemon, R.N. (1990). Non-invasive brain stimulation reveals reorganised cortical outputs in amputees. *Neuroscience Letters,* **116**, 379-386.

Hay, L. (1979). Spatio-temporal analysis of movements in children: Motor programs versus feedback in the development of reaching. *Journal of Motor Behavior,* **11**, 189-200.

Kaas, J.H., Merzenich, M.M., & Killackey, H.P. (1983). The reorganization of the somatosensory cortex following peripheral nerve damage in adult and developing animals. *Annual Review of Neurosciences,* **6**, 325-356.

Lashley, K.S. (1933). Integrative functions of the cerebral cortex. *Physiological Review,* **13**, 1-42.

Lajoie, Y., Paillard, J., Teasdale, N., Bard, C., Fleury, M., Forget, R., & Lamarre, Y. (1992). Mirror drawing in a deafferented patient and normal subjects: Visuoproprioceptive conflict. *Neurology,* **42**, 1104-1106.

Luria, A.R. (1973). *The working brain: An introduction to neuropsychology.* New York: Basic.

Merzenich, M.M., Kaas, J.J., Wall, J.T., Sur, M., Nelson, R.J., & Felleman, D.J. (1983). Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience,* **10**, 639-665.

Meulenbroek, R.G.J., & van Galen, G.P. (1986). Movement analysis of repetitive writing behavior of first second and third-grade primary school children. In H.S.R. Kao, G.P. van Galen & R. Hoosain (Eds.). *Graphonomics: Contemporary research in handwriting* (pp. 71-92). Amsterdam: North Holland.

Mulder, Th., & Geurts, A.C.H. (1993). Recovery of motor skills following following nervous system disorders: a behavioral emphasis. *Bailliere's Clinical Neurology,* **2**, 1-13.

Roelcke, U., Curt, A., Otte, A., Missimer, J., Maguire, R.P., Dietz, V., & Leenders, K.L. (1997). Influence of spinal cord injury on cerebral sensorimotor systems: A PET study. *Journal of Neurology, Neurosurgery and Psychiatry,* **62**, 61-65.

Sassoon, R., Nimmo-Smith, I., & Wing, A. (1986). An analysis of children's penholds. In H.S.R. Kao, G.P. van Galen, & R. Hoosain (Eds.) *Graphonomics: contemporary research in handwriting* (pp. 93-106). Amsterdam: North Holland.

Topka, H., Cohen, L.G., Cole, R.A., & Hallett, M. (1991). Reorganization of corticospinal pathways following spinal cord injury. *Neurology,* **41**, 1276-1283.

Traversa, R., Cicinelli, P., Bassi, A., Rossini, P.M., & Bernardi, G. (1997). Mapping of motor cortical reorganization after stroke: A brain stimulation study with focal magnetic pulses. *Stroke,* **28**, 110-117.

van Doorn, R.A. Keuss, P.J.G. (1993). Does the production of letter strokes in handwriting benefit from vision? *Acta Psychologica,* **82**, 275-290.

Wann, J.P. (1987). Trends in the refinement and optimization of fine motor trajectories: Observations from an analysis of the the handwriting of primary school children. *Journal of Motor Behavior,* **19**, 13-37.

Wiesendanger, M. (1998). Bernstein's principle of equal simplicity and related concepts. In M.L. Latash (Ed.), *Progress in motor control: Volume I: Bernstein's tradition in movement studies* (pp. 105-126). Champaign, IL: Human Kinetics.

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